# PATENT COOPERATION TREATY



# PCT

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference -861 | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/IL2004/000315 | International filing date *(day/month/year)* 07.04.2004 | Priority date *(day/month/year)* 08.04.2003 |
| International Patent Classification (IPC) or national classification and IPC C12N5/06, C07K14/00, A61K38/19 | | |
| Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 08.11.2004 | 30.06.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Telephone No. +49 89 2399- 8054 Nichogiannopoulou, A. |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000315

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-40 | as originally filed |
| **Claims, Numbers** | |
| 1-74 | as originally filed |
| **Drawings, Sheets** | |
| 1/3-3/3 | as originally filed |

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-26, 36-46, 71, 72 in respect to industrial application

because:

☒ the said international application, or the said claims Nos. 11-26, 36-46, 71, 72 in respect to industrial application relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. 25-36, 40-45, 47, 50-54

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000315

## Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. 1-24, 37-39, 46, 48, 49, 55 all completely and 25-36, 40-43, 45, 54 all partially .

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 10, 14, 22, 31, 34-46, 48, 49, 53, 54, 56-61, 65 |
| | No: | Claims | 1- 9, 11-13, 15-21, 23-30, 32, 33, 47, 50-52, 55, 62, 63, 66-74 |
| Inventive step (IS) | Yes: | Claims | 10, 14, 22, 31, 34-46, 48, 49, 53, 54, 56-61, 65 |
| | No: | Claims | 1- 9, 11-13, 15-21, 23-30, 32, 33, 47, 50-52, 55, 62, 63, 66-74 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 27-35, 47-70 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Supplemental Box relating to Sequence Listing

**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

## Re Item I

**Basis of the report**

1. The basis of this report is the application as originally filed.

## Re Item II

**Priority**

1. The following document was published prior to the international filing date but later than the priority date claimed (P-document):

   P1: KOLLET ORIT ET AL: "HGF, SDF-1, and MMP-9 are involved in stress-induced human CD34+ stem cell recruitment to the liver." JOURNAL OF CLINICAL INVESTIGATION, vol. 112, no. 2, July 2003 (2003-07), pages 160-169, XP002289611 ISSN: 0021-9738

2. The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (08.04.2003). If it later turns out that this assumption is incorrect, P1 will become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

## Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. Claims 11-26, 36-46, 71, 72 -as far as they concern *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV**

**Lack of unity of invention**

1. The present application is based on the finding that hepatic growth factor (HGF) upregulates CXCR4 expression which in turn functions as the stromal derived factor (SDF-1) receptor on haematopoietic stem cells. In effect, HGF promotes the SDF-1/CXCR4 dependent stem cell motility and migration to the target tissue. The present application separately claims general methods of treating a disorder by providing HGF. Finally stem cells and cell lines comprising nucleic acids encoding HGF are separately claimed.
Rule 13 PCT stipulates that the international application shall relate to one invention only or to a group so linked as to form a single general inventive concept. Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding "special technical features", i.e. technical features that define a novel and inventive contribution over the prior art (Rule 13.2 PCT). The common concept (technical relationship) linking the present claims together is that they all are concerned with HGF. However, this concept cannot be regarded as the "single general inventive concept" required by Rule 13 PCT because it is neither novel nor inventive. The prior art teaches uses of HGF as a colonisation composition promoting engraftment (WO 0250263), as a haematopoiesis augmenting factor (EP 0550769) and as a "mobilizer" of haematopoietic progenitors (US 5968501). Methods for increasing stem cell sensitivity to a chemoattractant are also known from the prior art (Pelled et al., 1999).
In view of the prior art the problems underlying the present application and their respective solutions can be seen as the following:

Problem 1: The provision of further methods for increasing sensitivity of stem cells to a chemoattractant. The solution to this problem is the subject of invention 1.

Problem 2: The provision of further uses of HGF. The solution to this problem is the subject of invention 2.

Problem 3: The provision of further cells and cell lines bearing nucleic acid constructs encoding HGF. The solution to this problem is the subject of invention 3.

Due the fact that the common concept cannot be regarded as special technical feature in the sense of Rule 13 PCT and due to the fact that no other "special"

technical feature (Rule 13.2 PCT) could be identified to provide a linking concept between the different groups of inventions, the International Searching Authority is of the opinion that there is no single inventive concept linking the present set of claims and the different inventions not belonging to a common inventive concept are formulated as the different subjects in the communication pursuant to Article 17(3)(a) PCT.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

D1: WO 02/50263 A (IMP COLLEGE INNOVATIONS LTD; FORBES STUART (GB); THEMIS MIKE (GB); TH) 27 June 2002 (2002-06-27)

D2: EP-A-0 550 769 (TORAY INDUSTRIES) 14 July 1993 (1993-07-14)

D3: NISHINO T ET AL: "HEPATOCYTE GROWTH FACTOR AS A HEMATOPOIETIC REGULATOR" BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, vol. 85, no. 11, 1 June 1995 (1995-06-01), pages 3093-3100, XP000564571 ISSN: 0006-4971

D4: US-A-5 968 501 (COMOGLIO PAOLO) 19 October 1999 (1999-10-19)

2. **Novelty and Inventive step** (Article 33(2) and (3) PCT)

2.1. The present application is based on the finding that hepatic growth factor (HGF) upregulates CXCR4 expression which in turn functions as the stromal derived factor (SDF-1) receptor on hematopoietic stem cells. In effect, HGF promotes the SDF-1/CXCR4 dependent stem cell motility and migration to the target tissue.

2.2. **D1** is an application disclosing the administration to a patient of a colonisation composition promoting engraftment or self-engraftment of bone-marrow derived stem cells into injured organs. This composition can be HGF (p. 4, l. 26, p. 5, l. 10 and p.22, l.21-22) and it can be recombinantely expressed by the stem cell itself (p. 3, l. 10-12 and p. 19, l.27 - p. 20, l.6) preferably under the control of an inducible promoter (p. 8, l.10 and p. 22, l. 2-3). **D1** is thus detrimental to the novelty and inventive step of claims 1-3, 5, 8, 9, 11-13, 15, 18-21, 23, 26, 47,

50-52, 55, 62, 66, and 69-71.

**D2** is a patent specification disclosing the use of hepatocyte growth factor to augment hematopoietic stem cell activity. No mention is made of the effect of HGF on CXCR4 expression on HSC but this is an inherent, albeit hitherto undisclosed, property of the treatment with HGF. Hence **D2** is detrimental to the novelty and inventive step of claims 1-7, 11-13, 15-17, 19-21, 23-25, 27-30, 32, 33, 62, 63, 66-68, and 71-74.

**D3** is a publication disclosing the role of HGF in hematopoiesis. It explicitly discloses the addition of HGF to long-term bone marrow and fetal liver cultures that inherently contain both hematopoietic and mesenchymal stem cells. Although the effect on CXCR4 was unknown at the time, it is an inherent feature of treating stem cells with HGF. **D3** is thus detrimental to the novelty and inventive step of claims 1-3, 5, 8, 62, 63, 66, and 69.

D4 discloses that HGF stimulates multipotent hematopoietic progenitors and that the HGF receptor is expressed on CD34 positive adult hematopoietic cells. HGF which can be used as a "mobilizer" of bone marrow precursors into the peripheral blood can also be administered to patients in need of hematopoietic stimulation. **D4** is thus detrimental to the novelty and inventive step of claims 1-6, 19-21, 23-25, 27-30, 32, 62-67, 71, 73, and 74.

3. **Industrial applicability** (Article 33(4) PCT)
The subject-matter of the claims for which an opinion has been established (see item III) appears to be industrially applicable under the terms of Article 33(4) PCT.